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RESEARCH ARTICLE

ADIPOQ and *ADIPOR2* gene polymorphisms: association with overweight/obesity in Mexican children

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KEYWORDS
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Abstract
Background: ENSANUT 2012 showed a combined prevalence of overweight and obesity of 34.4% in Mexican children. Single nucleotide polymorphisms (SNPs) of the *ADIPOQ* and *ADIPOR2* genes have been reported in many populations, but their association with obesity has not been confirmed in other studies. Our aim was to determine the association of SNPs from *ADIPOQ* and *ADIPOR2* genes with obesity in Mexican children.
Methods: A total of 2,634 children from 6 to 12 years old were enrolled in the study from four IMSS Units in Mexico City. We selected 1,469 unrelated children (745 normal weight and 724 overweight/obese). Phenotype characterization included anthropometric measurements, blood pressure, biochemical parameters, insulin concentrations and presence of acanthosis nigricans (AN). Analysis of the SNPs rs182052, rs266729, rs2241766, rs822393 of *ADIPOQ* and rs11061971 of *ADIPOR2* was carried out in the DNA samples.
Results: The study showed significant differences (p <0.05) between groups in waist circumference, blood pressure, presence of AN, insulin concentrations, HOMA-IR, fasting glucose and lipid parameters, being higher in obese children. No associations in *ADIPOQ* variants with the presence of overweight/obesity were found. The presence of the variant rs11061971 of *ADIPOR2* in children had a significant association with protection of overweight/obesity (OR 0.79, 95% CI 0.68-0.93, p = 0.003). Also, the log-additive model confirmed the association by codominant and dominant models (p <0.05).

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Conclusions: The presence of rs11061971 of *ADIPOR2* variant confers protection against obesity and could be used as a marker in Mexican children.

PALABRAS CLAVE
Obesidad infantil;
Adiponectina;
ADIPOQ;
ADIPOR2

Polimorfismos de los genes *ADIPOQ* y *ADIPOR2* y su asociación con sobrepeso/obesidad en niños mexicanos

Resumen
Introducción: ENSANUT 2012 mostró una prevalencia combinada de sobrepeso y obesidad en el 34.4% en niños mexicanos. Se han reportado polimorfismos de un solo nucleótido (SNP) de los genes *ADIPOQ* y *ADIPOR2* en varias poblaciones, pero su asociación con la obesidad ha sido controversial. El objetivo de este trabajo fue determinar la asociación de SNP de *ADIPOQ* y *ADIPOR2* con obesidad en una muestra de niños mexicanos.
Métodos: Un total de 2,634 niños de 6-12 años se inscribieron en el estudio en cuatro unidades del Instituto Mexicano del Seguro Social en la Ciudad de México. Se seleccionaron 1,469 niños no emparentados (745 peso normal y 724 sobrepeso/obesidad). Se les tomaron medidas antropométricas, presión arterial, parámetros bioquímicos, insulina y presencia de acantosis nigricans (AN). El análisis de los SNP (rs182052, rs266729, rs2241766, rs822393 de *ADIPOQ* y rs11061971 de *ADIPOR2*) se realizó en muestras de ADN.
Resultados: Se observaron diferencias significativas ($p < 0.05$) entre los grupos en la circunferencia de cintura, presión arterial, AN, insulina, HOMA-IR, glucosa en ayunas y parámetros lipídicos siendo elevados en los niños obesos. No se encontró asociación en variantes *ADIPOQ* con la presencia de sobrepeso/obesidad. La presencia de rs11061971 de *ADIPOR2* tuvo una asociación significativa con la protección de sobrepeso/obesidad (OR de 0.79; IC95% 0.68 a 0.93, $p = 0.003$). El modelo Log-aditivo confirmó la asociación de los modelos codominante y dominante ($p < 0.05$).
Conclusiones: La presencia de la variante rs11061971 de *ADIPOR2* confiere protección contra la obesidad, y podría utilizarse como marcador en niños mexicanos.

1. Introduction

Obesity is a public health problem that has increased dramatically in recent years, with epidemic proportions worldwide.[1–4] Obesity in Mexico is increased on average of 1.1 percentage points per year. The ENSANUT 2012 showed a combined prevalence of overweight and obesity of 34.4% in both sexes in children. It represents about 5,664,870 overweight and obese children in a national population.[5]

Many factors are associated with obesity in childhood, for example, lack of physical activity, diets with high content of carbohydrates and the genetic predisposition.[6,7] Previous studies have concluded that high concentration of adiponectin predict a lower prevalence of type 2 diabetes (T2D) in Mexican children[8] and that serum adiponectin can be a biomarker to predict metabolic syndrome in eutrophic and obese children.[9]

Adiponectin binds to its receptors (AdipoR1 and AdipoR2) for signaling actions. Adiponectin exhorts its effects through the sensitization of the body to the insulin[10,11] by activating numerous signaling molecules including adenosine monophosphate-activated protein kinase (AMPK), p38-MAPK, JNK, PPARα transcription factor and NF-κB in multiple tissues. These signals are transduced via the AdipoRs.[12,13] Mechanisms regulating the expression of AdipoRs appear to be complex and are governed by numerous factors.

The polygenic nature of obesity and the interactions of single nucleotide polymorphisms (SNPs) in overweight/obesity are not clear.[14] SNPs of the *ADIPOQ* gene have been reported in many populations; however, some of these associations with obesity could not be confirmed in other studies. The human *ADIPOR2* gene is generally not associated with serum adiponectin but is associated with insulin resistance and T2D risk in genetic association studies, but the mechanisms are not yet clear.[15–19]

The aim of present study was to determine the association of obesity with SNP variants rs182052, rs266729, rs2241766, rs822393 of *ADIPOQ* and the rs11061971 of *ADIPOR2* genes in Mexican children.

2. Methods

2.1. Participants

A total of 2,634 children from 6–12 years old were enrolled in the study from four IMSS Units in Mexico City: Cuauhtémoc, Nezahualcóyotl, Independence and Morelos (north, east, south, and northeast corresponding areas). A general description of the children studied is shown in Table 1. Children were randomly selected to participate in a cross-sectional study between July 2011 and July 2012.

Unrelated children (n = 1,469) were classified into normal weight (n = 745) and overweight/obesity (n = 724) groups according to their body mass index (BMI) percentile described by the U.S. Centers for Disease Control and Prevention (CDC). Children with autoimmune diseases, cancer or other diseases related to obesity were excluded. The study was conducted after informed consent was signed by parents and children, respectively. The National Committee and the Ethics Committee Board from the IMSS National Research Commission approved the protocol.

2.2. Procedure

Invitation for the study was conducted in each unit mentioned. The personnel enrolled in the project explained the benefits of participation in the study. Participants were evaluated with questionnaires and anthropometric measurements, and biochemical and genetic studies were applied. Each of the steps was performed according to related norms and clinical guidelines.

2.3. Clinical records

All participants were weighed using a digital scale (Seca, Hamburg, Germany). Height was measured with a portable stadiometer (Seca 225) and waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest after a normal exhalation with children in the standing position. Body mass index (BMI) was calculated and classified according to the CDC 2000 (Atlanta, GA, USA) references (eutrophic children 10th to <85th percentile, overweight children ≥85th to <95th percentile and obese children ≥95th percentile in BMI). Blood pressure was measured by auscultatory method using a mercurial sphygmomanometer (ALPK2, Tokyo, Japan) with appropriate cuff size for arm length following North American guidelines issued in 2004. Blood pressure readings were taken for each participant twice, on the right arm in a sitting position, resting 5 min between each measurement, and considering the level of blood pressure as the mean of the readings. The presence of acanthosis nigricans (AN) was recorded in the neck, armpit, under the breast or a skin crease and is described as positive if presented in any of the areas mentioned.

2.4. Biochemical studies

Blood samples were taken in children after a 12-h fast. Biochemical analysis included fasting glucose, total cholesterol, HDL-C and LDL-C and triglycerides using the ILab 350 Clinical Chemistry System (Instrumentation Laboratory IL, Barcelona, Spain). Insulin (μU/mL) was measured by chemiluminiscence (IMMULITE) and the HOMA-IR was calculated for insulin resistance.

2.5. Genotyping and genetic analysis

Genomic DNA was isolated from peripheral blood using a standard protocol for DNA extraction with a FLEX STAR Autogen (Holliston, MA). All samples were run in 0.8% agarose gels stained with ethidium bromide to verify the integrity and purity by 260/280 DO. We selected the most promising SNPs of the adiponectin gene and the receptor and minor allele frequencies ≥10% in the Mexican population according to the HapMap database. SNPs were rs182052, rs266729, rs2241766, and rs822393 of *ADIPOQ* and rs11061971 of *ADIPOR2*. Genotyping was performed using the TaqMan OpenArray Real-Time PCR System (Life Technologies, Carlsbad, CA) following the manufacturer's instructions. The genotype success rate was at least 98%, and no deviation ($p \geq 0.05$) from Hardy-Weinberg equilibrium was observed in the analysis. Thirty random samples were done in duplicate for genotype quality control with 100% concordance.

2.6. Statistical analysis

Tests were performed to check whether there were significant differences between cases and controls for the anthropometric and biochemical variables. Comparison between groups was done using the t test for continuous variables. For categorical data we used χ^2 test. Logistic regression models were performed to evaluate the association of overweight/obesity in different genotypes. We obtained odds ratios (OR) with 95% confidence intervals (CI) in the three main inheritance models: codominant, dominant and recessive, adjusted by age, gender and WHR. Statistical analysis was performed using STATA 11 software (Stata Corp LP, College Station, TX). We used the Stata program to estimate the statistical significance of p <0.05 and 95% CI in the study for each SNP with an expected OR of 1.2, 1.5, 2, 2.5; alpha = 0.05 and the minor allele frequency (MAF) for each SNP and each population in the study.

3. Results

Table 1 shows the general characteristics of the 2634 children studied. The presence of obesity ranged from 22-32% in the four units. Overweight and obesity was higher in Cuauhtémoc Unit, 23.27% and 32.50%, respectively, whereas the Independencia Unit showed the lowest percentage.

Table 2 shows the characteristics of the unrelated children (n = 1,469). The analysis comparison of normal weight children vs. overweight/obesity according to gender was similar in both groups. Family history of obesity was similar in children with normal weight and overweight/obese groups. The presence of AN was higher in the overweight/obesity group (p <0.0001). Waist circumference was significant (p <0.001) when comparing the groups and was 14 cm higher in children with overweight/obesity. Systolic and diastolic blood pressures were significant

Table 1 General characteristics of the four units from the IMSS (n = 2634).

BMI	IMSS unit				Total
	Cuauhtémoc	Nezahualcóyotl	Independencia	Morelos	
Underweight	6 (1.07%)	11 (2.06%)	15 (2.27%)	20 (2.28%)	52 (1.97%)
Normal weight	243 (43.16%)	277 (51.87%)	375 (56.82%)	477 (54.39%)	1372 (52.09%)
Overweight	131 (23.27%)	119 (22.28%)	124 (18.79%)	167 (19.04%)	541 (20.54%)
Obesity	183 (32.50%)	127 (23.78%)	146 (22.12%)	213 (24.29%)	669 (25.40%)
Total	563	534	660	877	2634 (100%)

Data represented in frequency and percentages by IMSS unit studied.

in children with overweight/obesity (p <0.001). Biochemical parameters showed statistical significance in fasting glucose and insulin measured by HOMA-IR in overweight/obese children. Lipids were elevated in children with overweight/obesity compared to normal weight children. Triglyceride concentration increased to 30 mg/dL in children with overweight and obesity.

Table 3 shows the allele frequencies and genotypes rs182052, rs266729, rs2241766, rs822393 of *ADIPOQ* and rs11061971 of *ADIPOR2* SNPs being displayed according to BMI children. All polymorphisms studied were in Hardy-Weinberg equilibrium (HWE).

Table 4 shows the effect of the five polymorphisms and the risk of overweight/obesity with ORs estimated through logistic regression adjusted by age, gender and family history of obesity. No association with obesity was shown in *ADIPOQ* SNPs, whereas the *ADIPOR2* rs11061971 polymorphism had a significant protective effect (OR 0.79, 95% CI 0.68-0.93, p = 0.003) in the log-additive model. This association was confirmed by codominant and dominant model (p <0.05).

4. Discussion

Adiponectin plays a role in obesity displaying anti-inflammatory and anti-atherogenic actions.[20–22] Several SNPs were reported associated in obese children; however, only few studies in Mexican children have been reported. We

Table 2 Clinical characteristics of unrelated children studied (n = 1469).

	Normal weight n = 745	Overweight/obesity n = 724	p value*
Gender (%)			
Female	50.76	50.43	
Male	49.24	49.57	0.89
Family history of obesity (%)			
Yes	42.72	41.49	<0.0001
No	58.51	57.28	
Presence of acanthosis nigricans (%)			
Yes	19.1	63.7	<0.0001
No	80.9	36.3	
Age (years)	9.12 ± 2.11	9.38 ± 2.03	<0.01
BMI (kg/m^2)	16.73 ± 2.11	22.69 ± 3.66	<0.001
WC (cm)	58.96 ± 7.04	74.36 ± 10.63	<0.001
DBP (mmHg)	64.47 ± 8.41	67.62 ± 8.41	<0.001
SBP (mmHg)	95.89 ± 10.35	101.12 ± 11.04	<0.001
FG (mg/dl)	81.96 ± 9.67	82.64 ± 9.35	<0.003
Insulin (IU/ml)	5.22 ± 4.12	10.18 ± 9.35	<0.001
HOMA-IR	1.03 ± 0.89	2.09 ± 2.10	<0.001
TC (mg/dl)	154.16 ± 31.93	162.18 ± 75.67	<0.006
TG (mg/dl)	76.65 ± 31.45	111.23±57.99	<0.001
HDL (mg/dl)	53.85 ± 12.35	47.08±12.37	<0.001
LDL (mg/dl)	98.07 ± 23.84	106.85±28.12	<0.001

Results are shown as percentages for categorical variables and mean ± standard deviation for continuous variables.
BMI, body mass index; WC, waist circumference; DBP, diastolic blood pressure; SBP, systolic blood pressure; FG, fasting glucose; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
* p values correspond to the t-test for age, Mann-Whitney U test for continuous variables and χ^2 for categorical variables.

Table 3 Genotypic, allelic frequencies and HWE of *ADIPOQ* and *ADIPOR2* genes.

Gen	SNP	BMI	Genotypes			Allele frequencies		HWE (*p* value)
ADIPOQ	rs182052		AA	AG	GG	A	G	
		All subjects	413 (29)	708 (49)	315 (22)	1534 (53)	1338 (47)	0.75
		Nw[a]	208 (29)	347 (47)	173 (24)	763 (52)	693 (48)	0.23
		Ow/Ob[b]	205 (29)	361 (51)	142 (20)	771 (54)	645 (46)	0.5
	rs266729		CC	CG	GG	C	G	
		All subjects	542 (38)	693 (48)	209 (14)	1777 (62)	1111 (38)	0.62
		Nw [a]	289 (40)	347 (47)	97 (13)	925 (63)	541 (37)	0.69
		Ow/Ob [b]	253 (36)	346 (49)	112 (15)	852 (60)	570 (40)	0.76
	rs2241766		TT	TG	GG	T	G	
		All subjects	940 (67)	431(30)	47 (3)	2311 (81)	525 (19)	0.86
		Nw [a]	476 (67)	214 (30)	27 (3)	1166 (81)	268 (19)	0.62
		Ow/Ob [b]	464 (67)	217 (30)	20 (3)	1145 (82)	257 (18)	0.45
	rs822393		CC	CT	TT	C	T	
		All subjects	414 (29)	699 (49)	329 (22)	1527 (53)	1357 (47)	0.32
		Nw	225 (30)	349 (48)	161 (22)	799 (54)	671 (46)	0.26
		Ow/Ob	189 (27)	350 (50)	168 (23)	728 (51)	686 (49)	0.82
ADIPOR2	rs11061971		TT	TA	AA	T	A	
		All subjects	589 (41)	661 (46)	186 (13)	1839 (64)	1033 (36)	1
		Nw	275 (38)	350 (48)	104 (14)	900 (62)	558 (38)	0.7
		Ow/Ob	314 (44)	311 (44)	82 (12)	939 (66)	475 (34)	0.74

The results are shown as numbers of patients for each genotype and allele frequency. Data in parentheses are given in percentages. HWE, Hardy-Weinberg equilibrium; BMI, body mass index; Nw, normal weight; Ow,Ob, overweight/obesity.

investigated the distribution of *ADIPOQ* and *ADIPOR2* polymorphisms in children from Mexico City. Our study showed no association between *ADIPOQ* gene variants in obesity. Only *ADIPOR2*, rs11061971 showed a protective association against obesity (Table 4).

Several reports showed an association of *ADIPOQ* gene variants with obesity or its comorbidities such as MetS. However, these results have not been convincing in replication studies in other populations; therefore, it seems to be playing an important role in the ancestry of the populations studied. Our study includes four different geographical regions of Mexico City where we observed differences in BMI prevalence.

Significant associations between obesity and polymorphisms in the gene coding for *ADIPOQ* have been reported in other studies. [23,24] Guzman-Ornelas et al. suggested that polymorphisms in the gene coding for *ADIPOQ* could be associated with distribution of body fat storage in adult obesity. On the other hand, no association was observed between gene polymorphisms and obesity in a Mexican-Mestizo population.[25]

The rs2241766 polymorphism of *ADIPOQ* has not been associated with obesity but has had significant associations in comorbidities such as MetS.[26] However, few studies have investigated the relationship between rs266729 polymorphism and risk of obesity or MetS. Regarding links between rs266729 and MetS, early studies reported varying results.[27,28] The rs182052 was associated with an increased risk of the prevalence of obesity in adult Korean women, but there were no significant interactions observed between the genotype of *ADIPOQ* rs182052 and dietary intake on BMI and body fat mass. These findings suggest that the obesity-related variables may be more dominantly affected by the genotype of *ADIPOQ* rs182052 than dietary intake in middle-aged Korean women. MAF in a Korean population (0.49) was different from European (0.40), Chinese (0.42) and Mexican (0.22) populations.[29] No study has reported the relationship between rs822393 of *ADIPOQ* and obesity. Ramya et al. in 2013 described that there was no association with T2D but there was an association with decreased adiponectin values.[30] On the other hand, the rs822393 of *ADIPOQ* was not associated in Mexican children.

The role of *ADIPOR2* in obesity could arise from the unique function of this receptor in mediating the effects of adiponectin in the liver. Adiponectin influences fat metabolism, increasing fatty acid oxidation through activation of AMP-activated protein kinase which, in turn, phosphorylates acetyl CoA carboxylase.[10] Lui et al. demonstrated a role of *ADIPOR2* in the pathogenesis of insulin resistance (IR) syndrome and T2D and suggest *ADIPOR2* as a promising target for the treatment of T2D patients, particularly those who have adiposity, IR and dyslipidemia.[18]

There are few studies of variant rs11061971 of *ADIPOR2* gene. No data exist in the National Center for Biotechnology

Table 4 Estimated effect of association by Mendelian inheritance model of *ADIPOQ* and *ADIPOR2* polymorphism with overweight/obesity.

Genes	SNP	Model	OR	95% CI	*p* value	P trend
ADIPOQ	rs2241766					
		T/T[c]	1			
		T/G[c]	1.05	0.83-1.32	0.74	
		G/G[c]	0.77	0.42-1.40	0.39	
		T/G + G/G[d]	1.02	0.81-1.27	0.89	0.82
		G/G[r]	0.76	0.42-1.37	0.36	
		Log-additive	0.98	0.81-1.19	0.86	
	rs822393					
		C/C[c]	1			
		C/T[c]	1.21	0.94-1.55	0.1	
		T/T[c]	1.23	0.91-1.65	0.15	
		C/T + T/T[d]	1.21	0.96-1.53	0.1	0.13
		T/T[r]	1.09	0.85-1.40	0.49	
		Log-additive	1.11	0.96-1.29	0.15	
	rs182052					
		G/G[c]	1			
		G/A[c]	1.06	0.83-1.36	0.59	
		A/A[c]	0.83	0.62-1.12	0.2	0.26
		G/A + A/A[d]	0.99	0.78-1.24	0.91	
		A/A[r]	0.8	0.62-1.03	0.08	
		Log-additive	0.92	0.79-1.07	0.28	
	rs266729					
		C/C[c]	1			
		C/G[c]	1.18	0.94-1.48	0.13	
		G/G[c]	1.31	0.95-1.81	0.11	0.07
		C/G + G/G[d]	1.21	0.97-1.50	0.09	
		G/G[r]	1.19	0.89-1.61	0.24	
		Log-additive	1.15	0.99-1.34	0.07	
ADIPOR2	rs11061971					
		T/T[c]	1			
		T/A[c]	0.74	0.59-0.93	0.01	
		A/A[c]	0.67	0.48-0.93	0.01	0.004
		T/A + A/A[d]	0.72	0.58-0.90	0.003	
		A/A[r]	0.78	0.57-1.07	0.12	
		Log-additive	0.79	0.68-0.93	0.003	

Results are described according to the models: [c]codominant, [d]dominant, [r]recessive and log-additive; adjusted by age, gender and family history of obesity.
SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

Information (NCBI) for the Mexican or Latino population. Studies in the Russian population showed that *ADIPOR2*, rs11061971 has an association with T2D.[19] Similarly, Damcott et al. reported that the T allele of rs11061971 was significantly associated with a higher risk of T2D.[31] The alleles of *ADIPOR2* forming the common haplotype AG were associated with a reduced risk of T2D. The protective role of this haplotype in the development of T2D could be attributed to its association with a decreased HOMA-IR value and, therefore, with reduced IR. In addition, the AG haplotype showed an association with lower serum concentrations of triglycerides. Other studies also found the relationship between multiple *ADIPOR2* variants and triglyceride levels but not with obesity.[32,33] *ADIPOR2* variant was observed as being protective for obesity in Mexican children.

The Mexican population is at relatively high risk for obesity, IR and T2D. The genetic variation in candidate genes of *ADIPOQ* and *ADIPOR2* could influence variation in such disease conditions and related traits. In the present study we provide evidence that the *ADIPOR2* polymorphism is associated with protection for obesity in Mexican children. Therefore, the presence of rs11061971 polymorphism of *ADIPOR2* could be used as a protective marker for obesity in children.

Conflict of interest

The authors declare there are no conflicts of interests of any nature.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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